Official Title: Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of EP547 in Subjects with Cholestatic Pruritus Due to Primary Biliary Cholangitis or Primary Sclerosing Cholangitis

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STATISTICAL ANALYSIS PLAN

Escient Pharmaceuticals, Inc.

EP-547-201

Protocol Title:	Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of EP547 in Subjects with Cholestatic Pruritus Due to Primary Biliary Cholangitis or Primary Sclerosing Cholangitis
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Prepared By:	[redacted]
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STATISTICAL ANALYSIS PLAN APPROVAL

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Emanate Biostats, Inc.

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ABBREVIATIONS

Table 1 List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike's information criterion
AKI	Acute kidney injury
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AR	First-Order Autoregressive
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
B2M	Beta-2-microglobulin
BLQ	Below the limit of quantification
BMI	Body mass index
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDCA	Chenodeoxycholic acid
CA	Cholic acid
CLU	Clusterin
CM	Composite measure
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CRO	Contract Research Organization
CS	Compound symmetry
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CysC	Cystatin-C
DCA	Deoxycholic acid
DILI	Drug-induced liver injury
D-FIS	Fatigue Impact Scale for Daily Administration
DMC	Data Monitoring Committee
DRT	Data Review Team
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EQ-5D-3L	3-Level EuroQol-5D
FC	Fold change
GCA	Glycocholic acid
GDCA	Glycodeoxycholic acid

Abbreviation	Definition
GCDCA	Glycochenodeoxycholic acid
GLCA	Glycolithocholic acid
GUDCA	Glycoursodeoxycholic acid
HEENT	Head, eyes, ears, nose, throat
IBD	Inflammatory bowel disease
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IL-31	Interleukin-31
IPD	Important Protocol Deviation
IWRS	Interactive Web Response System
KIM-1	Kidney injury molecule-1
LCA	Lithocholic acid
LLOQ	Lower limit of quantification
LS	Least-square
LSMD	Least-square mean difference
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputations
MMRM	Mixed effects model for repeated measures
NAG	N-acetyl-β-D-glucosaminidase
NGAL	Neutrophil gelatinase-associated lipocalin
OCA	Obeticholic acid
OLE	Open-Label Extension
OPN	Osteopontin
PBC	Primary Biliary Cholangitis
PD	Pharmacodynamic
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PROMIS	Patient-Reported Outcomes Information System
PSC	Primary Sclerosing Cholangitis
Q1	1st quartile (25th percentile)
Q3	3rd quartile (75th percentile)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA Query
TCA	Taurocholic acid
TCDCA	Taurochenodeoxycholic acid
TDCA	Taurodeoxycholic acid
TE	Transient elastography

Abbreviation	Definition
TEAE	Treatment-emergent adverse event
TLCA	Taurolithocholic acid
TTF3	Trefoil Factor 3
TUDCA	Tauroursodeoxycholic acid
UC	Ulcerative colitis
uCR	Urine creatinine
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
VAS	Visual analog scale
VEGF	Vascular endothelial growth factor
WHO	World Health Organization
WI-NRS	Worst Itch Numeric Rating Scale

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide comprehensive and detailed descriptions of the statistical methods and presentation of data collected for Escient Pharmaceuticals, Inc. Protocol EP-547-201 (Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of EP547 in Subjects with Cholestatic Pruritus Due to Primary Biliary Cholangitis or Primary Sclerosing Cholangitis). Descriptions of planned analyses are provided in order to avoid post hoc decisions that may affect the interpretation of the statistical analysis. The statistical methods applied in the design and planned analyses of this study are consistent with the International Council for Harmonisation (ICH) guideline *Statistical Principles for Clinical Trials (E9)* (1998) and *Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials (E9[R1], Rev 1)* (2021).

This SAP will be finalized prior to data analysis and before treatment unblinding and database lock to provide comprehensive details of the tables and listings to be presented in the Clinical Study Report (CSR). Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR. Minor changes or deviations from the templates for tables and listings need not be documented in the CSR.

2. STUDY OBJECTIVES

2.1 Primary Study Objective

The primary objective of this study is to assess the efficacy of EP547 compared to placebo on pruritus as assessed by the Worst Itch Numeric Rating Scale (WI-NRS).

2.2 Secondary Study Objectives

The secondary objectives of this study are:

- To assess the efficacy of EP547 compared to placebo on the following:
    - Pruritus-related quality of life using the 5-D Itch Scale
    - Pruritus severity using the Patient Global Impression of Severity (PGI-S)
    - Overall pruritus response to therapy using the Patient Global Impression of Change (PGI-C)
- To assess the safety and tolerability of EP547
- To assess the pharmacokinetics (PK) of EP547

2.3 Exploratory Objectives

[redacted]

[redacted]

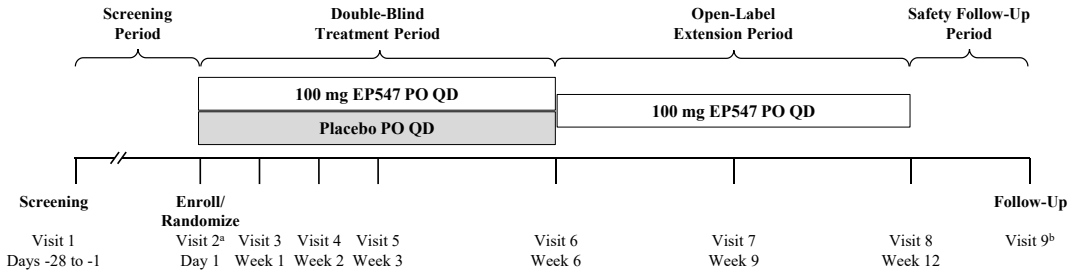
3. INVESTIGATIONAL PLAN

3.1 Overall Study Design

EP-547-201 is a randomized, double-blind, placebo-controlled study to evaluate the effects of EP547 on pruritus over 6 weeks in subjects with cholestatic pruritus due to primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC). Where allowed per regulatory/local requirements, subjects will be able to attend study visits at a physical study site as well as remotely (hybrid model) or at a virtual site where all visits will be conducted remotely (decentralized model). For both the hybrid and decentralized models, a home health nurse visit at the subject's home or work and a telemedicine visit with the study site staff (e.g., smartphone or computer) will be arranged to conduct procedures for each remote study visit.

The study includes a Screening Period of up to 4 weeks to assess subject eligibility; a 6-week Double-Blind Treatment Period; a 6-week Open-Label Extension (OLE) Period; and a 2-week Safety Follow-Up Period after administration of the last dose of study drug (EP547 or placebo). Approximately 58 subjects with cholestatic pruritus due to PBC or PSC will be randomized to receive either 100 mg doses of EP547 or placebo orally (PO) QD in a 1:1 ratio. In the Open-Label Extension Period, all subjects will receive 100 mg doses of EP547. Details of the study design are presented in Figure 1.

Figure 1 EP-547-201 Study Design



PO = oral, QD = once daily.

[a] For the decentralized model, enrollment/randomization and the first dose of study drug may be separated by up to 10 additional calendar days to allow for home delivery of study drug. When enrollment/randomization and first dose of study drug are on separate days, the first dose of study drug is considered Day 1.

[b] Any subject who completes the Open-Label Extension Period or discontinues study drug (EP547 or placebo) early will complete a follow-up visit approximately 2 weeks (±3 days) after the last dose of study drug.

The Screening Period will consist of one study visit (Visit 1). During this period, subjects will undergo assessments to determine study eligibility. Visit 1 (Day -28 to Day -1) may be conducted over more than one day but must be completed between Day -28 and Day -1.

The Double-Blind Treatment Period will consist of five study visits (Visits 2, 3, 4, 5, and 6 [Day 1 and Weeks 1, 2, 3, and 6]). During this period, all subjects who meet eligibility requirements will be enrolled into the study and randomized to receive double-blind, PO, QD 100 mg doses of EP547 or placebo for 6 weeks beginning on Visit 2 (Day 1). Visit 2 (Day 1) will not have a visit window; however, for the decentralized model, enrollment/randomization and the first dose of study drug may be separated by up to 10 additional calendar days to allow for home delivery of study drug. When enrollment/randomization and first dose of study drug are on separate days, the first dose of study drug is considered Day 1. All other visits in the Double-Blind Treatment Period will have a visit window of ±3 days.

For the hybrid model, Visits 1, 2, 6, and 8 (Screening, Day 1, Week 6, and Week 12) and early termination (if applicable) must be completed at the study site. All other study visits may be conducted remotely, where allowed per regulatory/local requirements. For the decentralized model, all visits will be conducted remotely.

For remote visits for both the hybrid and decentralized models, the home health nurse visit at the subject's home or work and the telemedicine visit with the study site staff for a given study visit may be conducted on different days but must be within the allowable visit window. The home health nurse will complete the study assessments that the site is physically unable to complete remotely (e.g., blood and lab sample collection, vital signs, electrocardiograms [ECGs]); the site will complete all other study assessments remotely during the telemedicine visit.

The Open-Label Extension Period will consist of two study visits (Visit 7 [Week 9] and Visit 8 [Week 12]). During this period, all subjects who complete the Double-Blind Treatment Period and are still receiving study drug will receive open-label 100 mg doses of EP547. Visit 7 and Visit 8 will have a visit window of ±3 days.

Any subject who completes the Open-Label Extension Period or discontinues study drug (EP547 or placebo) early will complete a Follow-Up Visit (Visit 9) approximately 2 weeks (±3 days) after the last dose of study drug.

3.2 Schedule of Assessments

For the complete schedule of assessments, refer to Appendix A of the clinical study protocol.

3.3 Treatments

3.3.1 Treatments Administered

Tablets containing 25 mg or 75 mg of EP547 or placebo will be supplied in a way to ensure the study blind. For the Open-Label Extension Period, tablets containing 25 mg and 75 mg of EP547 will be supplied. Subjects receiving EP547 will take one 25 mg

and one 75 mg EP547 tablet per dose (for a total dose of 100 mg) and subjects receiving placebo will take two placebo tablets per dose.

Each study drug dose, containing two tablets, is to be administered orally as intact tablets (swallowed whole, not chewed or crushed), and taken with water. Doses are to be administered daily at approximately the same time of day after a fast of at least eight hours.

EP-547-201 treatment assignments by study period are presented in Table 2.

Table 2 EP-547-201 Treatment Assignments

Study Period	Study Days	Approx. No. of Subjects	Treatment Designation	Study Drug Dose Regimen
Screening	Day -28 to Day -1	58	Not applicable	None
6-Week, Double-Blind Treatment	Day 1 to Day 42	29	100 mg EP547	One 25 mg EP547 tablet and One 75 mg EP547 tablet PO QD
		29	Placebo	Two placebo tablets PO QD
6-Week, Open-Label Extension	Day 43 to Day 85	58	100 mg EP547	One 25 mg EP547 tablet and One 75 mg EP547 tablet PO QD
2-Week Safety Follow-Up	2 weeks after last study drug dose	58	Not applicable	None

PO = oral; QD = once daily.

3.3.2 Prohibited Concomitant Medications

Subjects taking immunosuppressant/immunomodulating agents may not receive live, attenuated vaccines during participation in this study. Medications with known nephrotoxic potential (e.g., aminoglycosides, contrast dye, bisphosphonates, and nonsteroidal anti-inflammatory drugs) are prohibited from use during the study as are some medications that are substrates for BCRP, OAT1, CYP2B6, or CYP2C8, or inhibitors of OAT3. Table 3 of the clinical study protocol lists examples of excluded medications that are substrates for BCRP, OAT1, CYP2B6 or CYP2C8, or inhibitors of OAT3. If a subject receives a prohibited concomitant medication during the study, the Investigator, in consultation with the Medical Monitor, may interrupt or discontinue study drug as warranted for reasons of protecting subject safety.

3.3.3 Method of Assigning Subjects to Treatment Groups

All subjects who meet eligibility requirements will be enrolled into the study and randomized to receive double-blind, PO, QD doses of EP547 or placebo for 6 weeks beginning at Visit 2 (Day 1). Subjects will be randomized to receive either 100 mg doses of EP547 or placebo in a 1:1 ratio. Randomization will be conducted centrally via an Interactive Web Response System (IWRS) and stratified based on type of cholestatic disease (PBC or PSC).

All subjects who complete the Double-Blind Treatment Period and are still receiving study drug will receive open-label 100 mg doses of EP547 during the Open-Label Extension Period.

3.3.4 Blinding Procedures

The Sponsor, Medical Monitor, Contract Research Organization (CRO) staff, Investigators, site staff, and subjects will be blinded to subject's assigned treatment during the Double-Blind Treatment Period of the study until the database is locked except for CRO or vendor staff involved in the analysis of PK samples or safety reporting to regulatory agencies.

To address business needs, a limited number of study team members and senior stakeholders comprising the internal Data Review Team (DRT) may conduct and review an interim analysis of all accumulated data including unblinded data from the Double-Blind Treatment Period (see Section 4.4.7.3). The rest of the central study and project team members will remain blinded.

Treatment with 100 mg doses of EP547 during the Open-Label Extension Period will be conducted in an unblinded manner.

If an emergency unblinding during the Double-Blind Treatment Period is required, the subject's treatment assignment may be unblinded through IWRS by the Investigator. If a treatment assignment is unblinded, the subject will be discontinued from randomized treatment. Blinding codes should only be broken in emergency situations for reasons of subject safety and when knowledge of the treatment assignment will impact the clinical management of the subject. Every reasonable attempt should be made to complete the post-treatment evaluation procedures prior to unblinding as knowledge of the treatment arm could influence subject assessment.

In all emergency cases, the reasons and rationale for unblinding will be documented in writing and maintained in the study file.

Access to randomization codes and corresponding treatment assignment will also be made available through the IWRS system to the appropriate individual(s) responsible for unblinding suspected unexpected serious adverse reactions for reporting to the Regulatory Authorities.

3.4 Efficacy and Safety Variables

3.4.1 Efficacy Variables

3.4.1.1 Primary Efficacy Variable

The primary efficacy endpoint is the change from baseline in WI-NRS at Week 6.

Subjects will be asked to rate the severity of their worst level of itching in the past 24 hours in the morning, and at the same time of day, using the WI-NRS. The WI-NRS is an 11-point scale ranging from 0 (No Itching) to 10 (Worst Itching Imaginable) (Phan 2012) and requires approximately 1 minute to complete. Higher scores indicate greater itch severity. Itching severity scores collected via the WI-NRS have been categorized in the literature as mild (<4), moderate (≥4 to <7), or severe (≥7) (Fishbane 2020, Hirschfield 2020, Levy 2020, Stander 2020).

Subjects will be instructed to complete the WI-NRS daily, in the morning, and at the same time of day, beginning at Day -14 to the Follow-Up Visit. For days that coincide with a study visit (for Visit 2 and beyond), the WI-NRS is to be completed before the visit.

For WI-NRS, a weekly score will be determined based on the average of all available daily scores of the week. Weekly scores will be calculated for Week 1 through Week 6 of the Double-Blind Treatment Period and Week 7 through Week 12 of the Open-Label Extension Period. During the Safety Follow-up Period, weekly scores for Week 13 and Week 14 will be derived, when available.

The average WI-NRS score using the daily values from the week before the first dose of study drug (including the WI-NRS score captured on study day 1 of dosing) will serve as the baseline score.

For subjects who complete the nominal Week 6 visit, the weekly WI-NRS scores for both the Double-Blind Treatment Period and Open-Label Extension Period will be anchored to the nominal Week 6 visit date with the following considerations applied:

- Within the Double-Blind Treatment Period, analysis of Week 6 will be the 7 days leading up to the nominal Week 6 date (including the nominal Week 6 visit date WI-NRS score). Each preceding analysis visit will be the 7 prior days.

- Within the Open-Label Extension Period, analysis of Week 7 will be the first 7 days after the nominal Week 6 visit date or start date of open-label dosing, whichever is later; for subjects who participate in the decentralized model, there may be a gap between the nominal Week 6 visit and open-label dosing due to drug shipment considerations. Subsequent analysis visits will be counted using the next 7 days. The Week 6 WI-NRS score will be used as the Initiation of OLE score.

The Safety Follow-up Period will be anchored to the nominal Week 12 visit date. Week 13 will be the first 7 days after the nominal Week 12 visit date and Week 14 will be derived using the next 7 days.

For subjects who early terminate during the Double-Blind Treatment Period, the subject's first day of dosing (i.e., study day 1) will be the anchor date for weekly analysis visit derivations. Week 1 will be study days 2 through 8 and subsequent weekly analysis visits will be the next 7 days, deriving all applicable analysis visits until early termination.

The following additional general considerations will be applied in deriving the weekly WI-NRS scores:

- No WI-NRS daily score is to be utilized in more than one analysis visit derivation.

- For weeks where 7 calendar days are available for a given week, there must be 4 non-missing daily scores to compute the weekly score; if more than 3 daily scores are missing, the weekly score is considered missing.

- For weeks where less than 7 calendar days are available for a given week due to visit anchoring rules, at least 57% of the daily scores for the available calendar days must be reported, maintaining the same rate of reported scores as seen for a full week (i.e., 4 out of 7 days). If 6 calendar days are available for a given week, 4 non-missing daily scores are required. If 4 or 5 calendar days are available for a given week, 3 non-missing daily scores are required. If less than 4 calendar days are available for a given week, the weekly score will be considered missing.

A bi-weekly WI-NRS score will be calculated for exploratory analysis. The average WI-NRS score using the daily values from the 14 days before the first dose of study drug (including the WI-NRS score captured on the study day 1 of dosing) will serve as the baseline bi-weekly score.

Bi-weekly WI-NRS scores for Week 2, Week 4, and Week 6 in the Double-Blind Treatment Period and Week 8, Week 10, Week 12 in the Open-Label Extension Period and Week 14 in the Safety Follow-up Period will be calculated following the same general guidelines as the weekly WI-NRS scores, applied to a bi-weekly derivation (e.g., requiring 8 non-missing daily scores in 14 calendar days). For intervals shorter than 14 calendar days due to visit anchoring rules, at least 57% of the daily scores for the available calendar days must be reported for a bi-weekly score to be computed. The Change from OLE summary will be relative to the bi-weekly score prior to the Initiation of OLE (e.g., Week 6).

3.4.1.2 Secondary Efficacy Variables

All efficacy assessments will be performed as indicated in the Schedule of Assessments (Appendix A) of the clinical study protocol. Secondary efficacy endpoints include the following:

- Change from baseline in 5-D Itch Scale
- The proportion of subjects with improvement in pruritus as defined by PGI-C
- The proportion of subjects with improvement in pruritus severity from baseline as defined by change in PGI-S
- The proportion of subjects with a reduction in WI-NRS ≥2 from baseline
- The proportion of subjects with a reduction in WI-NRS ≥3 from baseline
- The proportion of subjects with a reduction in WI-NRS ≥4 from baseline
- The proportion of subjects with WI-NRS <4

5-D Itch Scale

The 5-D Itch Scale was developed as a brief but multidimensional questionnaire designed for pruritus that measures changes over time (Elman 2010). The 5 dimensions are degree, duration, direction, disability, and distribution. It requires approximately 1 to 2 minutes to complete. For analysis purposes, the single-item domain scores

(duration, degree and direction) are equal to the value indicated by the response choice, with a range of 1 to 5. The disability domain includes four items that assess the impact of itching on daily activities: sleep, leisure/social activities, housework/errands and work/school. The score for the disability domain is achieved by taking the highest score on any of the four categories. For the distribution domain, 16 body parts are listed to determine the distribution of itching over the last two weeks; the number of affected body parts is tallied (for a potential sum of 0 to 16) and the sum is sorted into five scoring thresholds: a sum of 0 to 2 is assigned a score of 1; a sum of 3 to 5 is assigned a score of 2; a sum of 6 to 10 is assigned a score of 3; a sum of 11 to 13 is assigned a score of 4, and a sum of 14 to 16 is assigned a score of 5. The scores of each of the 5 domains are achieved separately and then summed together to obtain a total 5-D score, ranging from 5 (no pruritus) to 25 (most severe pruritus).

PGI-C

Subjects will be asked to rate their impression of overall change in pruritus in the past 7 days compared to before they started taking study drug using the PGI-C. The PGI-C is a 7-point scale ranging from "Much Improved" to "Much Worse" and requires approximately 1 minute to complete (Guy 1976). Higher scores indicate less improvement in pruritus. For analysis purposes, subjects that report a change in their itch of "Minimally Improved" or better will be considered as being a responder for "improvement in pruritus" efficacy considerations.

PGI-S

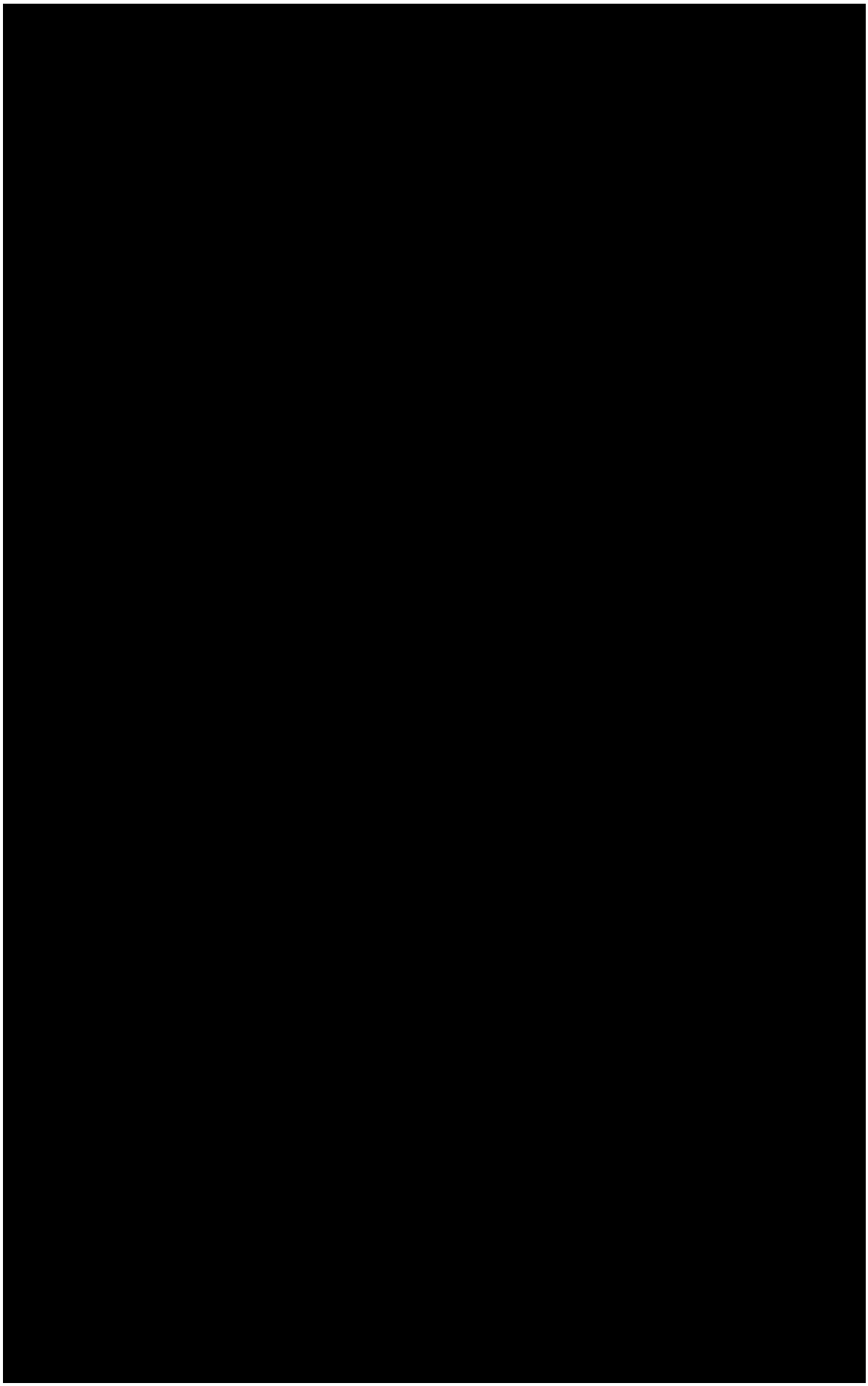
The PGI-S was validated in women with stress urinary incontinence, but may be used to rate the severity of other specific conditions (Yalcin 2003). For this questionnaire, the specific condition to be rated is pruritus. Subjects will be asked to rate the severity of their pruritus in the past 7 days using a 4-point scale from "None" to "Severe." The PGI-S requires less than 1 minute to complete. For analysis purposes, subjects that report a positive shift in their categorical assessment of itch compared to their baseline level (e.g., "Severe" at Visit 2 [Day 1] with a shift to "Moderate" at Visit 6 [Week 6]), will be considered a responder for "improvement in pruritus."

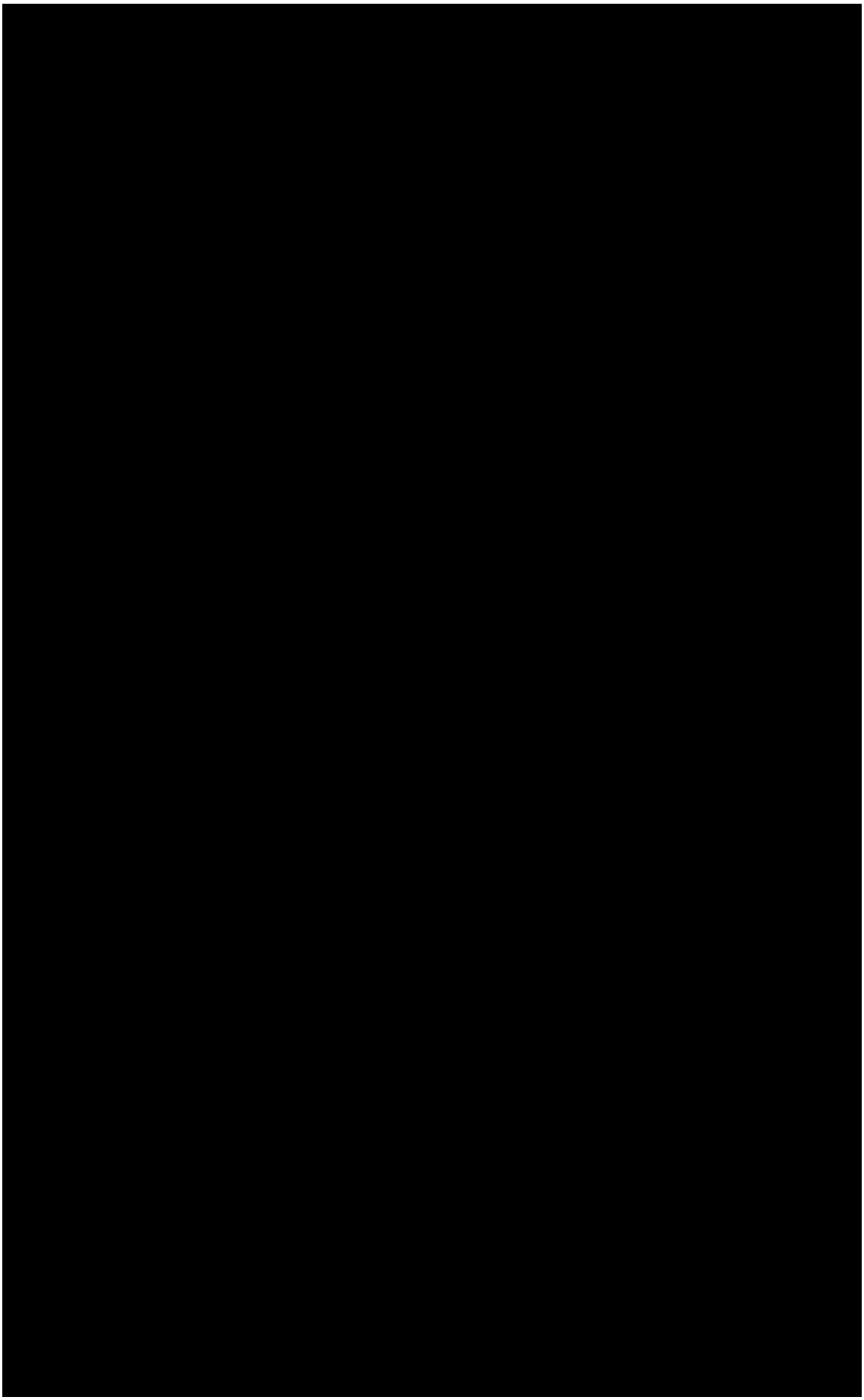
WI-NRS

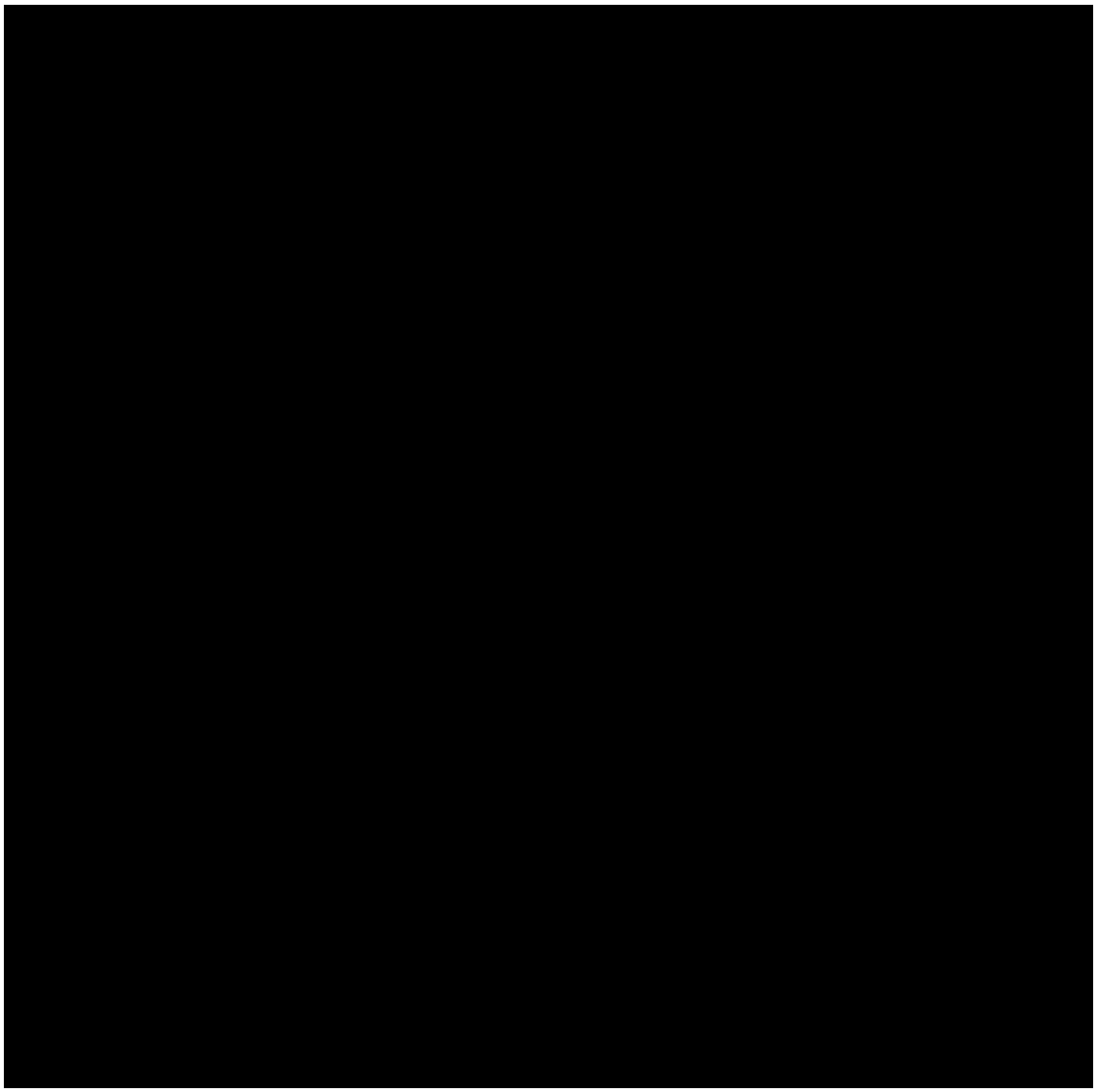
Details on the WI-NRS are described in Section 3.4.1.1.

3.4.1.3 Exploratory Efficacy Variables

[redacted]







3.4.3 Safety Variables

Safety evaluations, including adverse events (AEs), concomitant medications, medical history, vital signs, physical examinations, standard 12-lead ECGs, laboratory evaluations of safety, and disease-specific assessments (Partial Mayo Score for subjects with ulcerative colitis [UC] and Crohn's Disease Activity Index [CDAI] for subjects with Crohn's disease [CD]) will be performed as indicated in the Schedule of Assessments (Appendix A) of the clinical study protocol. For the decentralized model, the Investigator may require the subject to have an in-person consultation with a physician after virtually conducting safety assessments, if deemed necessary.

3.4.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. All AEs are recorded in the source documents and in the electronic case report forms (eCRFs) provided by

the Sponsor from the signing of the Informed Consent Form (ICF) until the end of study participation.

Medical conditions present at baseline that worsen in severity or frequency after exposure to study drug are considered treatment-emergent AEs (TEAEs). Planned hospital admissions or surgical procedures for an illness or a disease that existed before administration of study drug, and for which the condition has not worsened since starting study drug, are not to be considered TEAEs/treatment-emergent serious AEs (SAEs). Events with emergency room visits that are less than 24 hours will also not be considered SAEs unless they meet one of the criteria listed in Section 12.2.1 of the clinical study protocol.

Clinically significant abnormal laboratory tests, 12-lead ECG assessments, or vital sign results may, in the opinion of the Investigator, constitute an AE. However, whenever possible, the underlying diagnosis should be listed in lieu of associated abnormal results. Abnormalities deemed not clinically significant by the Investigator should not be reported as AEs.

Subjects will be assessed for potential drug-induced liver injury (DILI) during both the Double-Blind Treatment Period and Open-Label Extension Period according to the consensus guidelines for clinical trials in adults with chronic cholestatic liver disease (Palmer 2020). Monitoring, interrupting, and stopping rules based on multiples of upper limit of normal (ULN), threshold values, baseline values, and/or nadir values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin and liver- related symptoms are described in the algorithms for treatment-emergent hepatocellular and cholestatic DILI signals in Section 12.13.3 of the clinical study protocol.

Adverse events are graded for severity (i.e., intensity) using the U.S. Department of Health and Human Services Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (HHS 2017). All AEs will be assessed for relationship to study drug based upon the definitions provided in Section 12.1.3 of the clinical study protocol.

Any clinically meaningful new, worsening from baseline, or abnormal laboratory findings or symptoms suggestive of acute kidney injury (AKI) (e.g., ‘blood urea increased’ or ‘protein urine present’ AEs as identified by the Standardized Medical Dictionary for Regulatory Activities [MedDRA] Query [SMQ] ‘acute renal failure’) will be considered AEs of special interest (AESI).

An SAE is any untoward medical occurrence, that at any dose:

- Results in death;
- Is life-threatening, i.e., the subject is, in the opinion of the Investigator, at immediate risk of death from the event as it occurred (it does not include an event that, had it occurred in a more severe form, might have caused death);
- Requires hospital admission or prolongs hospitalization. Planned hospital admissions or surgical procedures for an illness or a disease that existed before administration of study drug, and for which the condition has not worsened

since starting study drug, are not to be considered SAEs. Emergency room visits that are less than 24 hours will also not be considered SAEs;

- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly/birth defect; or
- Is a medically significant event that, based on appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

3.4.3.2 Safety Laboratory Parameters

Samples for the following laboratory tests will be collected after an overnight fast (at least 8 hours):

- Chemistry: sodium, albumin, ALP, bicarbonate, calcium, bile acids, corrected calcium, chloride, total and direct bilirubin, AST, ALT, blood urea nitrogen, urea, creatinine, magnesium, phosphorus, potassium, creatine phosphokinase, glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, lactate dehydrogenase, gamma-glutamyltransferase, and total protein
- Hematology: hemoglobin, hematocrit, white blood cell counts with differential (lymphocytes, neutrophils, monocytes, eosinophils, and basophils), red blood cell count, platelet count, and platelet volume. If a subject develops lymphopenia, blood lymphocytes will be tested to assess populations of circulating T cells (including CD4+ and CD8+ subtypes), B cells, and natural killer cells.
- Urinalysis: leukocyte esterase, nitrites, pH, protein, specific gravity, glucose, occult blood, ketones, bilirubin, urobilinogen, albumin, creatinine, sodium, chloride, and potassium; microscopic analysis is to be performed only if protein, leukocyte esterase, blood or nitrite is positive
- Coagulation: activated partial thromboplastin time, international normalized ratio, and prothrombin time
- Pregnancy testing: required for all females; serum test at Screening (Visit 1) and urine test for all other visits where pregnancy testing is required
- Thyroid function tests: thyroid-stimulating hormone and free thyroxine

The urine pregnancy test for female subjects will be conducted locally; all other planned laboratory evaluations of safety will be conducted at a central laboratory.

3.4.3.3 Vital Signs

Vital signs, including sitting systolic and diastolic blood pressure, pulse rate, oxygen saturation, body temperature, and respiratory rate, will be measured after at least 5

minutes of rest. Vital signs are to be performed pre-dose if the dose is administered at the site.

Vital signs also include body weight, which should be measured with no shoes on and using a calibrated scale throughout the study.

3.4.3.4 Physical Examinations

Physical examinations will include, but are not limited to, an assessment of general appearance, skin, head, eyes, ears, nose, throat (HEENT), musculoskeletal, thyroid/endocrine, cardiovascular, chest/lung, neurologic, abdomen, and extremities/general body systems. Symptom directed physical examinations to assess clinically significant changes from Screening or any new signs or symptoms may be conducted at other visits as determined by the Investigator based on subject complaint. Any clinically significant findings will be recorded as medical history (prior to first dose) or adverse events (post first dose).

For the decentralized model, the Investigator, assisted by the mobile nurse, will conduct physical examinations per protocol via telemedicine during a videoconference session.

3.4.3.5 Standard 12-Lead Electrocardiograms

Twelve-lead ECGs are to be performed with subjects in a supine position after at least 5 minutes of rest.

3.4.3.6 Partial Mayo Scoring Index (Subjects with Ulcerative Colitis Only)

The Partial Mayo Scoring Index is a non-invasive questionnaire used as an outcome measure for clinical studies assessing therapies for UC (Lewis 2008). The index is composed of 3 categories (Bleeding, Stool Frequency, and Physician Assessment) that are each rated from 0 to 3 and summed to give a total score that ranges from 0 to 9. The Partial Mayo Scoring Index will be used to monitor disease stability during the course of the study.

3.4.3.7 Crohn's Disease Activity Index (Subjects with Crohn's Disease Only)

The CDAI is a composite instrument used for evaluating the disease severity of CD that is scored on a scale from 0 to 1100 and includes abdominal pain, general well-being, complications, abdominal mass, anemia, and weight change. Subjects with CD can be divided into asymptomatic remission (CDAI <150), mild-to-moderate CD (150 to 219), moderate-to-severe CD (220 to 450), and severe-fulminant disease (>450) (Chen 2018). The CDAI will be used to monitor disease stability during the course of the study.

3.4.3.8 Other Safety Screening Assessments

During the Screening Period, subjects will undergo assessments to determine their study eligibility. The following additional safety assessments not already described above are to be performed at Screening:

- Samples for the following laboratory tests will be collected after an overnight fast (at least 8 hours): immunoglobulin G4 and serology (human

immunodeficiency virus, hepatitis A virus, hepatitis B virus, hepatitis C virus, and hepatitis E virus)

- Transient elastography (TE): FibroScan TE. If an eligible historical TE within 6 months of Screening is not available, TE procedures will be conducted at study sites with the appropriate equipment and by adequately trained study site staff. Scheduling of the TE assessment should be within the Screening window (Day -28 to Day -1).

- SARS-CoV-2 Testing (Only required prior to protocol amendment version 3.0): Subjects will be tested for SARS-CoV-2 (coronavirus disease 2019 [COVID-19]) at Screening via reverse transcription-polymerase chain reaction test. A positive test result for COVID-19 will exclude the subject from enrolling in the study, even if the subject is asymptomatic, regardless of vaccination status.

3.4.4 Pharmacokinetic Variables

Blood sampling for PK of EP547 will be collected pre-dose and [redacted] to analyze EP547 concentrations; the metabolite profile may also be analyzed from these samples. The PK will be evaluated based on plasma concentrations of EP547 and potential metabolite profile.

In the event of an SAE, the Investigator should collect, if at all possible, a blood PK sample at an unscheduled visit as part of SAE follow-up.

3.5 Data Quality Assurance

Report summaries will be generated using validated Base SAS® software, version 9.4 or higher, on a PC or server-based platform. Additional validated software may be used to generate analyses, as needed.

All SAS programs that create outputs or supporting analysis datasets will be validated by a second statistical programmer or biostatistician. At a minimum, validation of programs will consist of a review of the program log, review of output or dataset format and structure, and independent confirmatory programming to verify output results or dataset content. Additionally, all outputs will undergo a review by a senior level team member before finalization.

The content of the source data will be reviewed on an ongoing basis by project statistical programmers and statisticians. Data will be checked for missing values, invalid records, and extreme outliers through defensive programming applications, analysis-based edit checks, and other programmatic testing procedures. All findings will be forwarded to the project data manager for appropriate action and resolution.

4. STATISTICAL METHODS

4.1 General Methodology

Data will be analyzed by Emanate biostatistics personnel. Statistical analyses will be reported with tables and listings, presented in rich text format, and using recommended

ICH numbering. Output specifications for all tables and listings will be in conformance with guidelines specified by the ICH in Appendix 7 of the Electronic Common Technical Document Specification (Apr 2003).

4.1.1 Reporting Conventions

In general, tables will be summarized by treatment group and overall. Summaries will be presented for both the Double-Blind Treatment Period and the Open-Label Extension Period separately. Tables summarizing data from the Open-Label Extension Period will summarize subjects by randomized treatment from the Double-Blind Treatment Period as well as by all subjects combined. In general, all data collected and any derived data will be presented in subject data listings, for all enrolled subjects. Listings will be ordered by site, subject number, treatment group, and assessment or event date. The treatment group presented in listings will be based on the planned assignment, unless otherwise noted.

In general, continuous variables will be summarized to indicate the study population sample size (N), number of subjects with available data (n), mean, SD, median, first (Q1) and third (Q3) quartiles, minimum, and maximum values. Categorical variables will be summarized by the population size (N), number of subjects with available data (n), number of subjects in each category, and the percentage of subjects in each category. Unless otherwise noted, the denominator to determine the percentage of subjects in each category will be based on the number of subjects with available data. Select ordinal data may be summarized using both descriptive statistics and counts and percentages of subjects in each category, as appropriate.

Non-zero percentages will be rounded to one decimal place. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (i.e., on the eCRF or as provided within an external file) and are outlined as follows:

- The mean and median will be rounded to one more decimal place than the precision of the variable of summarization;
- Measures of variability (e.g., SD, SE) will be rounded to two more decimal places than the precision of the variable of summarization; and
- Minimum and maximum values will be presented using the same precision as the variable of summarization.

Other statistics (e.g., CIs) will be presented using the same general rules outlined above, or assessed for the most appropriate presentation based on the underlying data.

Statistical significance testing will be two-sided and performed using $\alpha=0.05$. P-values will be reported for all statistical tests, rounded to four decimal places. P-values less than 0.0001 will be displayed as "<0.0001"; p-values greater than 0.9999 will be displayed as ">0.9999".

4.1.2 Definition of Baseline

Baseline will be defined as follows:

- For WI-NRS analysis, the average WI-NRS score using the daily values from the week before the first dose of study drug (Visit 2 [Day 1]) will serve as the baseline score. The WI-NRS value reported on Visit 2 [Day 1] is to be collected prior to the study visit according to the clinical study protocol and will be used in the baseline derivation. Day -6 through Day 1 will reflect the seven days of data reporting to be utilized.

- [redacted], the average WI-NRS score using the daily values from the 14 days before the first dose of study drug (including the WI-NRS score captured on the study day 1 of dosing) will serve as the baseline bi-weekly score.

- For all other study assessments, baseline is the last pre-treatment value available prior to the first dose of study drug.

Change from baseline summaries of the Open-Label Extension Period will utilize the same baseline definition derived in the Double-Blind Treatment Period. Change from the initiation of OLE will also be summarized for the Open-Label Extension Period summaries; change from the initiation of OLE will compare OLE assessments with the subject's Week 6 [Visit 6] reported assessment or last available measurement in the event Week 6 is not reported.

4.1.3 Summarization by Visit

Assessments that are collected only at study visits (i.e., all study assessments except WI-NRS) are to be summarized by study visit and will be based on the nominal, scheduled visit label as reported on the eCRF.

Subjects who discontinue from the study early will have their assessments conducted at the early termination visit mapped and summarized with the next scheduled nominal visit, according to the schedule of events, based on the last visit completed per protocol.

Any subject who completes the Open-Label Extension Period or discontinues study drug (EP547 or placebo) early will complete a Follow-Up Visit (Visit 9) approximately 2 weeks (±3 days) after the last dose of study drug. The Follow-Up Visit may be summarized in both the Double-Blind Treatment Period and Open-Label Extension Period summaries, based on the treatment period of participation at the time of study termination or completion and as warranted by available data.

Data collected at unscheduled visits will not be included in by-visit summaries, but will be considered when endpoint derivations potentially include multiple visits (e.g., determination of baseline value, determination of worst post-baseline value, etc.). All data will be included in subject listings.

For details on WI-NRS analysis visits, see Section 3.4.1.1.

4.1.4 Data Handling Rules

Unless otherwise noted, values reported as greater than or less than some quantifiable limit (e.g., "< 1.0") will be summarized with the sign suppressed in summary tables,

using the numeric value reported. Data will display on subject listings to include the sign.

4.1.5 Standard Calculations

Where appropriate, the calculated study day of each assessment or event will be presented with the assessment or event date on subject data listings, where study day will be determined as:

- The assessment/event date minus the date of first dose of study drug, if the assessment/event date is prior to the date of first dose; and

- The assessment/event date minus the date of first dose of study drug, plus one, if the assessment/event date is on or after the date of first dose.

Other variables requiring calculations will be derived using the following formulas:

- **Days:** A duration between two dates expressed in days will be calculated using the following conventions:

    - Later date – earlier date + 1, if the earlier date is on or after the reference date of interest (e.g., date of first dose of study drug); or

    - Later date – earlier date, if the earlier date is prior to the reference date of interest.

- **Months:** A duration expressed in months will be calculated by dividing the duration in days by (365.25 / 12).

- **Years:** A duration expressed in years will be calculated by dividing the duration in days by 365.25.

- **Change from Baseline:** Change from baseline will be calculated as the post baseline value minus the baseline value.

- **Percentage Change from Baseline:** Percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100.

4.2 Analysis Sets

The analysis sets are defined as follows for the Double-Blind Treatment Period:

- Full Analysis Set: All subjects who are randomized and take at least 1 dose of randomized study drug will be included in the Full Analysis Set. Subjects in the Full Analysis Set will be analyzed according to randomized treatment assignment. If a subject is incorrectly stratified (i.e., randomized according to an incorrect stratification), the subject will be analyzed under the randomized treatment for the stratum recorded in the IWRS. All efficacy and PD analyses will be based on the Full Analysis Set.

- Per Protocol Set: The Per Protocol Set is a subset of the Full Analysis Set containing subjects who meet study eligibility requirements and have no protocol deviations that might impact the assessment of efficacy measurements. Subjects will be analyzed according to randomized treatment assignment. The Per Protocol Set will be used for sensitivity analyses relating to efficacy and PD. Protocol deviations that qualify for exclusion from the Per Protocol Set include:

    - Deviations of inclusion/exclusion criteria
    - Non-permitted concomitant medications that may meaningfully impact efficacy outcomes (e.g., receipt of prohibited and/or a rescue medication qualifying as an intercurrent event)
    - Meaningful dosing and/or randomization error(s)
    - Any other important protocol deviation deemed by the Sponsor to warrant exclusion from the Per Protocol set

  Any protocol deviations that govern exclusion from the Per Protocol Set will be determined prior to database lock and primary analysis.

- Safety Analysis Set: All subjects who are randomized and take at least 1 dose of randomized study drug will be included in the Safety Analysis Set. Safety analyses will be based upon treatment actually received.

- PK Set: All subjects who receive at least 1 dose of EP547 and provide adequate blood samples for bioanalysis will be included in the PK Set.

Data summaries to be presented on both the Safety Analysis Set and the Full Analysis Set will only be produced on both analysis sets if there is a difference in the population groups.

An Open-Label Extension Analysis Set will be determined as all subjects who complete the Double-Blind Treatment Period and receive at least one dose of study drug in the Open-Label Extension Period and will be used to summarize all available data collected in both the Double-Blind and Open-Label Extension Periods.

4.3 Study Subjects

4.3.1 Disposition of Subjects

Subject disposition will be summarized for all randomized subjects by treatment group and over all subjects combined, separately for the Double-Blind Treatment Period and Open-Label Extension Period. Summaries will include the number and percentage of subjects in each analysis set, completing treatment within each study treatment period, completing the study, and the reason for discontinuation from each treatment period and the overall study. Subject disposition during the Double-Blind Treatment Period will also be summarized separately for each study site for all randomized subjects.

The number and percentage of subjects randomized by geographic region, country and site will be presented by treatment group and over all randomized subjects in the Double-Blind Treatment Period.

The number and percentage of screen failures will be presented by screen failure reason, based on the total number of subjects screened.

4.3.2 Protocol Deviations

Important Protocol Deviations (IPDs) will be summarized by treatment group and over all subjects combined for the Full Analysis Set. Important Protocol Deviations are identified by the Sponsor and are defined in the ICH guideline *Structure and Content of Clinical Study Reports – Questions and Answers (E3[R1], 2013)* as a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

All IPDs will be determined and appropriately categorized prior to database lock and prior to breaking the blind of the treatment group assignments. The number and percentage of subjects with any IPDs as well as the number and percentage of subjects with IPDs within each category will be presented. A listing of important protocol deviations will be provided.

4.4 Efficacy and Pharmacodynamic Evaluation

4.4.1 Datasets Analyzed

All efficacy and PD summaries will be based on the Full Analysis Set; select efficacy summaries will also be produced on the Per Protocol Set. In general, the Double-Blind Treatment Period summaries will summarize subjects by treatment group; the Open-Label Extension Period will summarize subjects by randomized treatment from the Double-Blind Treatment Period as well as by all subjects combined. A data listing of subjects excluded from the Full Analysis Set or Per Protocol Set, to include the reason for exclusion, will be presented. The efficacy and PD endpoints will be further evaluated during the Open-Label Extension Period with descriptive statistics for the Open-Label Extension Analysis Set; summaries of change over time will evaluate both change from baseline and change from the initiation of OLE.

4.4.2 Demographic and Other Baseline Characteristics

Demographic variables including age, sex, ethnicity and race will be summarized by treatment group and over all subjects combined for the Safety Analysis Set, Full Analysis Set, Per Protocol Set, PK Set, and the Open-Label Extension Analysis Set. Demographics will be also analyzed by the stratum factor, cholestatic liver disease type.

Age will be summarized using descriptive statistics. Sex, ethnicity, and race will be summarized with the number and percentage of subjects in each parameter category. Age, ethnicity and race will also be presented in the subgroup categories described in Section 4.4.7.8 with the number and percentage of subjects in each subgroup category.

Baseline characteristics include medical history, itch history, disease characteristics, transient elastography (FibroScan TE), estimated glomerular filtration rate (eGFR) height, weight, and body mass index (BMI). Body mass index will be calculated as: weight (kg) / [height (cm) / 100]^2. Baseline characteristics will be summarized for the Full Analysis Set by treatment group and over all subjects combined. Height, weight, BMI, Fibroscan, and eGFR at baseline will be summarized using descriptive statistics. Baseline eGFR will also be presented categorically by the subgroups (<90 vs ≥ 90 mL/min/1.73 m^2) described in Section 4.4.7.8 with the number and percentage of subjects in each subgroup summarized.

Baseline disease characteristics to be summarized include time since initial cholestatic disease diagnosis, type of cholestatic disease, presence of inflammatory bowel disease (IBD), type of IBD, use of obeticholic acid (OCA), and use of UDCA at baseline. Time since initial cholestatic disease diagnosis (in years) is calculated as the informed consent date – the date of diagnosis divided by 365.25. Time since initial cholestatic disease diagnosis will be summarized using descriptive statistics. Type of cholestatic disease, presence and type of IBD, baseline/concurrent OCA and baseline/concurrent UDCA use will be summarized with the number and percentage of subjects in each parameter category.

Itch history will be summarized for the Full Analysis Set with the number and percentage of subjects in each parameter category of the following itch history questions:

- Did the subject have significant itch or periods of consistent itch prior to liver disease diagnosis? (Yes / No)
- Is the itch worse during the: Day / Night / No Difference
- Itch Frequency (Daily / Near-Daily / Other)
- Does Itch Interfere with Sleep (Yes / No)
- Areas of Body that are Itchy (Face / Chest / Abdomen / Back / Limbs / Palms / Soles / Scalp / Other Body Area)
- Secondary Lesions Present (Yes / No)
- Itch More Prominent in Different Seasons (Yes / No)
- Season(s) Where Itch is Worse (Winter / Spring / Summer / Autumn)
- Circumstances that Aggravate Itching (Heat / Cold / Stress / Eating / Physical Activity / Showering / Clothing / Menstrual Period / Other)
- Subject Tried Treatment in the Past? (Yes / No)
- Did Past Treatment Help? (Yes / No)

Baseline height, weight, BMI, Fibroscan, eGFR, disease characteristics, and itch history summarizations will be repeated for the Safety Analysis Set, Per Protocol Set, PK Set,

and for the Open-Label Extension Analysis Set. Baseline characteristics of height, weight, BMI, Fibroscan, eGFR, and disease characteristics will be also analyzed by the stratum factor, cholestatic liver disease type.

Medical history conditions will be mapped to preferred terms and system organ classes using MedDRA, version 25.0. Frequency counts and percentages to summarize subjects reporting abnormal medical history by system organ class will be presented for the Full Analysis Set.

4.4.3 Primary Efficacy Endpoint Analysis Methods

The primary estimand is the difference in means between treatment groups in the weekly WI-NRS score at Week 6 for all subjects in the Full Analysis Set. The treatment policy strategy for addressing intercurrent events will be used for the primary estimand; data collected following use of prohibited and/or rescue medications or for subjects who prematurely discontinue from study drug use will be reported in the analysis. The WI-NRS data will be analyzed using a mixed effects model for repeated measures (MMRM) based on the data from weekly scores up to Visit 6 (Week 6) in the Double-Blind Treatment Period. The model will include treatment, type of cholestatic disease (PBC, PSC), week, and treatment by week interaction as fixed effects, and the baseline WI-NRS weekly score as a covariate. The unstructured covariance model will be used. In the event the computational algorithm fails to converge, the following structures will be executed: heterogeneous Toeplitz, Toeplitz, heterogeneous First-Order Autoregressive [AR(1)], AR(1), heterogeneous compound symmetry (CS), and CS. The covariance structure converging to the best fit, as determined by Akaike's information criterion (AIC), will be used. The Kenward-Roger approximation will be used to calculate the denominator degrees of freedom for the test of fixed effects. The null hypothesis to be tested is that there is no difference between EP547 and Placebo:

$$H_0: \mu_A = \mu_B;$$

Where μ_A and μ_B represent the mean values for EP547 and Placebo, respectively. The alternate hypothesis to be tested is that the treatment group means differ:

$$H_1: \mu_A \neq \mu_B;$$

Testing of the hypothesis is 2-sided at a 5% type I error level. Estimates of least-square (LS) means, standard error, and 95% CIs will be presented by treatment group. In addition, the LS mean difference (LSMD) of the comparison between EP547 and placebo, the standard error of the difference, and 95% CI of the difference will be presented.

Percent change from baseline will also be analyzed in the Double-Blind Treatment Period and Open-Label Extension Period. Descriptive statistics will be provided for weekly WI-NRS scores in the Double-Blind Treatment Period and Open-Label Extension Period summaries, to include the observed weekly value, change from baseline, percent change from baseline, change from initiation of OLE and percent change from initiation of OLE (in OLE-specific summaries). Initiation of the OLE is considered the Visit 6 (Week 6) average score, or the last available weekly score if Week 6 is not reported. In addition, a categorical summary of WI-NRS by itch severity (mild as defined as <4, moderate as defined as 4 to <7, and severe as defined as ≥7) will

be provided for each week. Normality assumptions will be assessed for appropriateness. If any are violated and inhibit the interpretation of the results, appropriate data transformations or non-parametric analyses will be performed in addition to other planned sensitivity analyses to support the interpretation of the treatment effect. If the model does not converge under the covariance structure testing methods, a reduced model restricted to select analysis visits (i.e., Week 1, Week 2, Week 3, and Week 6) or analysis of covariance (ANCOVA) model (with treatment group as a fixed effect and the randomization strata type of cholestatic disease [PBC, PSC] and covariate adjustment for baseline WI-NRS score) may be explored post-hoc.

4.4.4 Secondary Endpoint Analysis Methods

Analysis of secondary endpoints will be performed on the Full Analysis Set. Treatment group comparisons will be tested at the 5% significance level without multiplicity adjustment.

4.4.4.1 5-D Itch Scale

The change from baseline in 5-D Itch Scale total score will be analyzed using an ANCOVA model with fixed effects for treatment group and randomization strata (type of cholestatic disease [PBC, PSC]) and covariate adjustment for baseline 5-D total score. Descriptive statistics will be presented for values and changes from baseline for all post baseline visits where data was scheduled to be collected. The LS means and SE will be presented for all treatment groups. The LSMD and their SEs, 95% CIs, and p-value to test for a difference between EP547 to placebo at Week 6 will also be presented for the Double-Blind Treatment Period. Descriptive statistics will also be presented for individual component scores.

Descriptive statistics will be presented for the Open-Label Extension Period to include change from baseline and change from initiation of OLE.

4.4.4.2 Responder PGI-C Analysis

The proportion of subjects with improvement at Week 6 will be compared among treatment groups using a Cochran-Mantel-Haenszel (CMH) chi-square test, stratified by the type of cholestatic disease (PBC, PSC). The PGI-C responses at each visit in the Double-Blind Treatment Period (i.e., Week 6) and Open-Label Extension Period (i.e., Week 12) will also be presented with the number and percentage of subjects in each response category by treatment group along with two-sided 95% Clopper-Pearson exact CIs. Proportional endpoints (PGI-C, PGI-S and WI-NRS) will be analyzed using the number of patients in each treatment group with non-missing data at each visit (i.e., observed values) as the denominator for percentages for the Double-Blind Treatment Period and Open-Label Extension Period summaries.

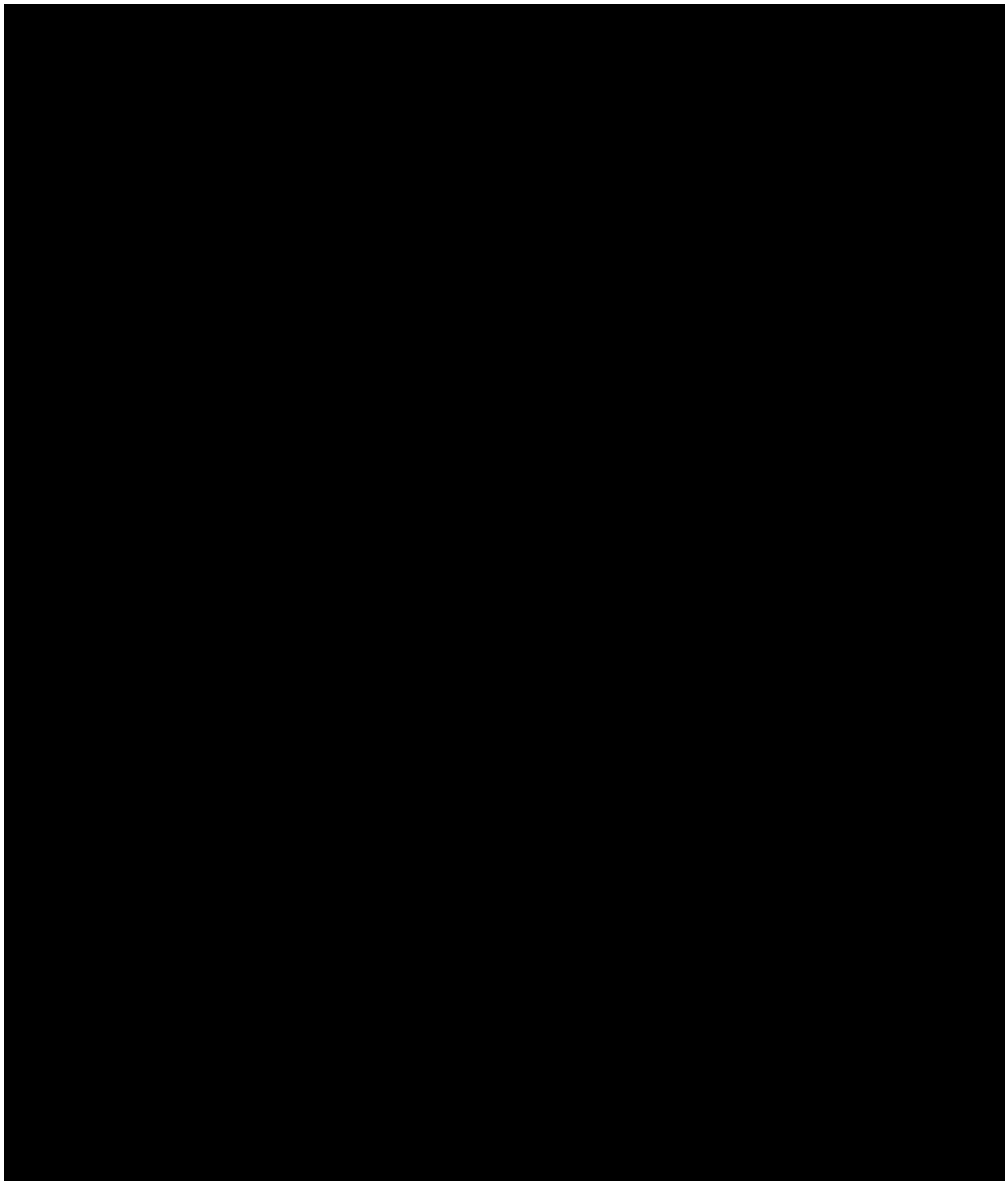
4.4.4.3 Responder PGI-S Analysis

The PGI-S improvement in pruritus severity will be analyzed using the same statistical methodologies as the PGI-C analysis described in Section 4.4.4.2. The proportion of subjects with improvement in pruritus at Week 12 relative to their initiation of OLE value will also be summarized.

4.4.4.4 Responder WI-NRS Analysis

The proportion of responders in WI-NRS will be analyzed using the same statistical methodologies as the PGI-C analysis described in Section 4.4.4.2. The proportion of subjects with a reduction in WI-NRS score of ≥2, ≥3 and ≥4 when compared to baseline and those with WI-NRS score <4 will be assessed at each analysis visit during the Double-Blind Treatment Period and Open-Label Extension Period to include the Safety Follow-Up weeks. The proportion of subjects within each WI-NRS category will also be assessed relative to their initiation of OLE value for visits in the Open-Label Extension Period and Safety Follow-Up visits.

4.4.5 Exploratory Endpoint Analysis Methods



4.4.6 Sensitivity Analysis of Efficacy Endpoints

Sensitivity analyses of the primary endpoint will be conducted to better assess the impact of intercurrent events on the efficacy conclusions. The intercurrent events of interest include receipt of prohibited and/or rescue medications while on study and early withdrawal of study drug. The treatment policy strategy will be used for the primary estimand.

The while on treatment strategy will be used as a sensitivity analysis to further explore the intercurrent event of prohibited and/or rescue medication usage. The difference in means between treatment groups in the weekly WI-NRS score at the last visit prior to receipt of prohibited and/or rescue medications (or the last derived weekly WI-NRS score, for those who never require prohibited and/or rescue medication) will be presented during the Double-Blind Treatment Period. For those subjects that receive a prohibited and/or rescue medication, any WI-NRS scores reported after the receipt of medication will be excluded from the analysis.

Determination of intercurrent events based on use of a prohibited and/or rescue medication will be based on review of the Concomitant Medication eCRF. Before study unblinding, the sponsor will review all reported concomitant medications, including on-study changes to background medications, to determine which qualify as an intercurrent event for prohibited or rescue medication usage. This external assessment will be documented in the study files and integrated into the sensitivity analysis.

The analysis of the primary efficacy endpoint will be analyzed for the Full Analysis Set using multiple imputations (MI) assuming data missing at Week 6 to be missing at random (MAR) (Section 4.4.7.2), and for the Per Protocol Set using observed data.

Treatment group comparisons will use the methodology described in Section 4.4.3 for sensitivity analysis of the primary endpoint.

Secondary and PD endpoint analyses during the Double-Blind Treatment Period will be repeated for the Per Protocol Set as supportive analyses.

4.4.7 Statistical/Analytical Issues

4.4.7.1 Adjustments for Covariates

The MMRM or ANCOVA model (depending on the endpoint) to compare treatment groups during Double-Blind Treatment Period will include a covariate adjustment for the baseline parameter value of interest.

4.4.7.2 Handling of Dropouts or Missing Data

Treatment groups will be compared for observed and change from baseline in weekly WI-NRS score during the Double-blind Treatment Period using a MMRM to include fixed effects for treatment, type of cholestatic disease (PBC, PSC), week, and treatment by week interaction, with the relevant baseline value included as a covariate. A similar model will be used for the exploratory analysis of bi-weekly WI-NRS scores, replacing the week score with a bi-weekly score in the model.

As a sensitivity analysis of the primary endpoint, subjects missing data will be imputed using MI methodology using the subjects in the Full Analysis Set. The MI will be performed under the assumption data is missing at random (MAR) using the model defined in the primary analysis. Using the general methodology described in Ouyang (2017), the following imputations will be applied:

- Intermittent missing value(s) arising prior to a discontinuation event (i.e., discontinuation of randomized treatment or early permanent dropout) are imputed using the Markov Chain Monte Carlo (MCMC) option in SAS PROC MI by treatment group assuming nonmonotone missing, a seed of 671982, 500 burn-in iterations, 100 iterations between imputations, and a non-informative prior. The MAR assumption is reasonable for intermittent missing values as the values of the endpoint before and after the intermittent missing value are known. The imputation of the intermittent missing data will be accomplished using the MCMC option in SAS PROC MI to impute intermittent missing data without a monotone missing pattern, prior to performing imputations of values following the discontinuation event.

- Missing data following a discontinuation event will then be imputed by treatment group under the assumption of MAR using the regression option from the monotone statement of SAS PROC MI. The baseline and post-baseline derived weekly visits during the Double-Blind Treatment Period will be used in the regression option to impute the missing values.

- The MI methods described above will be used to generate 30 imputed datasets. Data will be analyzed using the primary MMRM model for the observed and imputed data; observed and change from baseline values to each post-baseline week visit will be calculated based on observed and imputed data.

- Results from the analysis of each of the 30 imputed datasets will be combined using Rubin's imputation rules (Rubin 1987) through SAS PROC MIANALYZE to produce pooled LS mean estimates of treatment difference.

For assessment of responder endpoints, subjects with missing data at the time point of interest will not be analyzed (i.e., PGI-C, PGI-S and WI-NRS); only observed values will be used.

4.4.7.3 Planned Interim, Primary, and Final Analyses and Data Monitoring

To address business needs, an interim analysis may be conducted after approximately 50% of randomized subjects have completed 4 weeks of randomized treatment. Only a limited number of study team members and senior management stakeholders comprising the internal DRT would review the results of the interim analysis of unblinded data from the Double-Blind Treatment Period. The interim analysis would evaluate the effect of EP547 on WI-NRS, select secondary endpoints, and safety.

The primary analysis will be conducted after the last subject randomized has completed the Double-Blind Treatment Period to determine whether the primary efficacy endpoint of change from baseline in WI-NRS at Week 6 is statistically significant. Details regarding the primary analysis procedures, including database lock and unblinding procedures, will be finalized prior to analysis.

The final analysis will be conducted when all randomized subjects have completed the Open-Label Extension Period or are discontinued from the study, and the final database is locked.

The Data Monitoring Committee (DMC) is an independent group of external experts who will review safety data during the conduct of the study, as outlined in the DMC charter. The DMC will make a determination of relatedness for all AEs with CTCAE Grade 3 or higher. The DMC will also meet on an ad hoc basis when at least 3 AEs of CTCAE Grade 3 or higher have accrued or when there has been a single CTCAE Grade 4 or higher. Based on review of the data, the DMC will provide recommendations to the Sponsor on whether the nature, frequency, and/or severity of AEs associated with study drug warrant modification to the study protocol, suspension of dosing, or study termination.

4.4.7.4 Multicenter Studies

This is a multicenter study to be conducted globally. Efficacy data collected from all study sites will be pooled for data analysis. The effect of study site on the efficacy analysis results may be explored post-hoc, as needed.

4.4.7.5 Multiple Comparisons/Multiplicity

This is the first study to explore the efficacy of EP547 for more than 7 days. The familywise error rate will be controlled for the primary efficacy endpoint at an alpha of 5%. All other efficacy endpoints will be tested at the 0.05 level of significance without multiplicity adjustment.

4.4.7.6 Use of an "Efficacy Subset" of Subjects

The primary efficacy analysis will be performed on the Full Analysis Set; the Per Protocol Set will be utilized as a sensitivity analysis. The Per Protocol Set will exclude subjects with protocol deviations that might impact the assessment of efficacy measurements.

4.4.7.7 Active-Control Studies Intended to Show Equivalence

This study does not include an active-control product and is not intended to demonstrate equivalence between any two drug products.

4.4.7.8 Examination of Subgroups

The primary efficacy endpoint and select secondary efficacy endpoints will be analyzed based on:

- Age (< 65 years of age vs ≥ 65 years of age)
- Gender (Male vs Female)
- Race (White vs All Other Races)
- Ethnicity (Hispanic or Latino vs Not Hispanic or Latino)
- Cholestatic liver disease type (PBC or PSC)
- Prescence of IBD (Yes or No)
- IBD Type (CD or UC)
- OCA use at baseline (Yes or No)
- Geographic region (North America vs Europe/Rest of the World)
- Baseline itch severity (moderate/WI-NRS <7 vs severe/WI-NRS ≥7)
- Any improvement in PGI-C (Week 6 for Double-Blind Treatment Period; Week 12 for Open-Label Extension Period [Open-Label Extension Analysis Set only])

The primary and select secondary efficacy endpoints to include the WI-NRS responder analysis will be analyzed for the subgroups using the Full Analysis Set and the Open-Label Extension Analysis Set. Separate summaries will be presented for each subgroup category.

Select safety analysis defined in Section 4.5.3 and 4.5.5 will be analyzed by the following subgroups:

- Cholestatic liver disease type (PBC or PSC)
- Baseline eGFR (<90 vs ≥90 mL/min/1.73 m^2)

A summary of subject disposition will also be provided by each subgroup. Demographic and baseline characteristics will be further explored by the stratum factor, cholestatic liver disease type. Summaries by subgroup will only be produced if there are at least 5 subjects in the category of interest for each treatment group. Additional subgroup analyses may be performed post-hoc, as appropriate.

4.4.8 EP547 Plasma Concentrations

Raw plasma concentration values will be summarized for the PK Set by treatment group and sampling time point in the Double-Blind Treatment Period using descriptive statistics, to include the geometric mean and CV (%). The geometric CV is calculated as 100*sqrt[exp(σ^2)-1], where σ^2 is the variance of the log-transformed data. For summaries of plasma concentrations, BLQ values will be set to missing. The number and percentage of subjects with BLQ values will be summarized by time point and treatment group.

4.4.9 Pharmacokinetic Analysis

Pharmacokinetic analysis will be based on analysis of the EP547 concentration data as outlined in Section 4.4.8.

4.5 Safety Evaluation

Safety analyses during the Double-Blind Treatment Period will be carried out for the Safety Analysis Set, to include all subjects who receive at least one dose of study drug. Safety analyses during the Double-Blind Treatment Period and Open-Label Extension Period will be summarized for the Open-Label Extension Analysis Set, to include all subjects who receive at least one dose of study drug during open-label participation. Safety data will be summarized separately for the Double-Blind Treatment Period and Open-Label Extension Period by randomized Double-Blind treatment received; a summary of all subjects combined within each study treatment period will also be provided. Subjects who do not complete the study, for whatever reason, will have all available data up until the time of termination included in the analysis. For safety analysis presented by study visit, the baseline value will be defined as described in Section 4.1.2 to include a Change from Baseline and Change from Initiation of OLE assessment.

4.5.1 Extent of Exposure

Extent of exposure to study treatment will be summarized by treatment group separately for each study treatment period as well as over the entire study participation. The duration of exposure will be presented in days and calculated as the date of last dose of study drug of the respective study treatment period minus the date of first dose of study drug of the respective study treatment period, plus one. For the purposes of defining the start of the Open-Label Extension Period, the on-site dose from the Week 6 Study Drug Administration (On-site) eCRF will be considered the start of OLE dosing for the duration of exposure calculation in the Open-Label Extension Period. The Open-Label Extension Period summary will also include a summary of duration of exposure across all study participation (both study treatment periods).

As dosing includes receipt of a 25 mg and 75 mg tablet for each daily dose totaling 100 mg of study drug, the total number of tablets received in each study treatment period will be determined based on treatment period dosing ranges as described in Section 4.5.2 (Treatment Compliance) and dosing will be based on the number of tablets received with the following derivation:

- Subjects reporting an even number of tablets will have their total dose received (mg) calculated as: (total tablets taken during study treatment period divided by 2) multiplied by 100.

- Subjects reporting an odd number of tablets (i.e., there was an incomplete dosing day) will have their total dose received (mg) calculated as: (the floor of [total tablets taken during study treatment period divided by 2] multiplied by 100) + 25 mg.

Duration of exposure and total dose received (mg) will be summarized using descriptive statistics. The Open-Label Extension Period summary will also include a summary of total dose received for EP547 across both study treatment periods for those randomized to EP547.

4.5.2 Measurements of Treatment Compliance

Compliance to the study treatment regimen will be summarized by treatment group, separately for each study treatment period as well as over the entire study participation. Compliance will be determined based on tablet count entries made on the Study Drug Dispensing and Accountability eCRF pages. Expected dosing will be based on the on-site dosing administration:

- The expected tablet dosing for Double-Blind Treatment Period is considered to be the on-site dose from Day 1 to the Treatment Completion or Treatment Discontinuation Date on the End of Treatment (Double-Blind eCRF), plus 1. The number of dosing days is then multiplied by two to account for two tablets of EP-547 or placebo taken each day.

- The expected tablet dosing for Open-Label Extension Period is considered to be the on-site dose from the Week 6 Study Drug Administration (On-site) eCRF to the Treatment Completion or Treatment Discontinuation Date on the End of Treatment (Open-Label eCRF), plus 1. The number of dosing days is then multiplied by two to account for two tablets of EP-547 taken each day.

The actual number of doses (tablets) received will be determined based on the number of tablets taken reported on the Study Drug Dispensing and Accountability eCRF. The number of tablets taken in the Double-Blind Treatment Period and Open-Label Extension Period will be assessed based on the defined treatment period windows (using the date ranges calculated in the expected dosing derivation) and the kit dispense dates.

Treatment compliance will then be calculated as the actual number of tablets taken divided by the expected number of tablets taken, multiplied by 100 for each treatment period and overall.

The number and percentage of subjects who are < 80% compliant and ≥ 80% compliant within each treatment group will be summarized separately for each study treatment period, as well as for overall study participation.

4.5.3 Adverse Events

Treatment-emergent adverse events are defined as those AEs with onset after the first dose of study drug or existing events that worsened after the first dose during the study. Treatment-emergent AEs will be summarized by treatment group separately for each study treatment period and overall, within each study treatment period. An overall TEAE summary, incidence of TEAEs by system organ class and preferred term, and summary of the most frequently-occurring TEAEs will also be presented for both periods combined (i.e., overall study) for the Safety Analysis Set and the Open-Label Extension Analysis Set. Adverse events will be considered treatment-emergent relative to the study treatment period where the onset of the AE occurred; any TEAE that begins in the Double-Blind Treatment Period will be considered treatment-emergent in the Double-Blind Treatment Period only. The same logic is to be applied to the Open-Label Extension assessment; the Week 6 Study Drug Administration (On-site) entry will be considered the start of Open-Label Extension dosing for assessing treatment-emergence. Events reported with a partial onset date (e.g., month and year are reported but the day is missing) will be considered to be treatment-emergent in both treatment periods if it cannot be confirmed that the event onset was prior to the first dose of study drug for a specific treatment period based on the available date entries. Events with date and time present will be compared against the treatment start date and time to determine treatment-emergence.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using MedDRA, version 25.0.

Summaries that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class and preferred term within each system organ class. Summaries displayed by preferred term only will be ordered by descending incidence of preferred term. Inclusion criteria assessments for frequency-related summaries will be made separately for each study treatment period and study overall. Summaries of the following types will be presented:

- Overall summary of number of unique TEAEs and treatment-emergent SAEs and subject incidence of TEAEs meeting various criteria;
- Subject incidence of TEAEs by MedDRA system organ class and preferred term;
- Subject incidence of the most frequently-occurring TEAEs (i.e., TEAEs occurring in ≥ 10% of the Safety Analysis Set or Open-Label Extension Analysis Set) by MedDRA preferred term;
- Subject incidence of TEAEs by CTCAE severity grade, MedDRA system organ class, and preferred term;

- Subject incidence of TEAEs by relationship to study drug, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs of Special Interest by MedDRA system organ class and preferred term;
- Subject incidence of the most frequently-occurring TEAEs related to study drug (i.e., related TEAEs occurring in ≥ 10% of the Safety Analysis Set or Open-Label Extension Analysis Set) by MedDRA preferred term;
- Subject incidence of CTCAE grade 3 or higher TEAEs related to study drug by MedDRA system organ class and preferred term; and
- Subject incidence of SAEs by MedDRA system organ class and preferred term.

A summary by safety subgroups of interest (type of cholestatic disease and baseline eGFR) described in Section 4.4.7.8 will be provided for the overall AE summary and subject incidence of TEAEs by MedDRA system organ class and preferred term for the Double-Blind Treatment Period, Open-Label Extension Period, and study overall.

At each level of summarization (e.g., any AE, system organ class, and preferred term), subjects experiencing more than one TEAE will be counted only once. In the summary of TEAEs by severity grade, subjects will be counted once at the highest severity reported at each level of summarization; in the summary of TEAEs by relationship, subjects will be counted once at the closest relationship to study drug. Related events include those reported as "Related" to study drug; events considered not related are those reported as "Not Related" to study drug.

Adverse event data will be presented in data listings by subject, treatment group, and event. Serious AEs and AEs leading to discontinuation of the study drug will be presented in separate data listings.

4.5.4 Deaths, Other Serious Adverse Events, and Adverse Events of Special Interest

All deaths during the study will be listed by subject, to include the primary cause of death. Serious AEs and AEs of Special Interest, including those that led to withdrawal, or interruption of the study drug, will be provided in separate subject data listings.

4.5.5 Clinical Laboratory Evaluation

All descriptive summaries of laboratory results will be based on data analyzed by the central laboratory and presented in conventional units. All data will be included in by-subject data listings. Laboratory measurements identified as abnormal (i.e., outside the normal range) will also be listed separately by subject, laboratory test, and unit. In addition, normal ranges provided by the central laboratory will be presented in a separate listing.

Clinical laboratory measurements, including serum chemistry, hematology, coagulation, and thyroid function tests, will be summarized by treatment group and all subjects combined for each study treatment period. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters

were scheduled to be collected per the clinical study protocol. A summary by safety subgroups of interest (type of cholestatic disease and baseline eGFR) described in Section 4.4.7.8 will be provided for the univariate summaries of chemistry and hematology using the Safety Analysis Set and Open-Label Extension Analysis Set. Change from the initiation of OLE will also be presented in the Open-Label Extension Period summaries.

Where applicable, laboratory results will be classified as "low," "normal," or "high" with respect to the parameter-specific reference ranges (i.e., below the lower limit of the normal range, within the normal range, or above the upper limit of the normal range). Three-by-three contingency tables will be presented for each laboratory parameter to summarize the shift from the baseline category to the worst post-baseline measurement within each treatment period, defined as the value numerically farthest outside of the normal range across all post-baseline visits through the end of each study treatment period and the study overall. Shift from the initiation of OLE value to the worst post-OLE value will also be provided for the Open-Label Extension Period. Summary results will include the count and percentage of subjects within each shift category and treatment group separately for each study treatment period and the study overall.

Where applicable, hematology, chemistry and coagulation results for select parameters will be assigned a toxicity grade based on the U.S. Department of Health and Human Services CTCAE, version 5.0 (HHS 2017). If criteria for a grade includes a quantitative component and a clinical intervention component, the clinical intervention component will be ignored where it cannot be programmatically addressed using available data and only the quantitative portion of the criteria will be considered. If the quantitative criteria for grading are equivalent for two grades and the differentiation is described by clinical interventions, the clinical intervention component will not be considered and the highest CTCAE grade will be assigned. Similarly, death related to AE (i.e., Grade 5) cannot be determined with available laboratory-based data collection and, thus, will not be summarized as a category. Laboratory parameters that include multiple sets of criteria for each direction (e.g., separate criteria for potassium measures to assess hyperkalemia and hypokalemia) will be summarized separately to reflect each set of criteria.

Five-by-five contingency tables will be presented for lab tests where toxicity grading can be applied, to summarize the shift from the baseline grade to the worst post-baseline grade within each study treatment period and the study overall. Grades will be presented as none (Grade 0; i.e., measurements did not meet any CTCAE criteria for Grades 1 through 4), mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). Shift from the initiation of OLE value to the worst post-OLE value will also be provided for the Open-Label Extension Period. Summary results will include the count and percentage of subjects within each shift category, analyzed separately for each study treatment period.

The clinical study protocol includes algorithms for monitoring and interrupting study drug for treatment-emergent hepatocellular and cholestatic DILI signals based on ALT, ALP and total bilirubin values. A shift from baseline in ALT or ALP values to select treatment-emergent DILI signal criteria will be summarized for each study period and the study overall.

Subjects with post-baseline ALT values will be assessed for shift from Baseline ALT to the following DILI criteria:

Normal Baseline ALT:

- Any Instance of ALT ≥ 3 x ULN and Total Bilirubin ≥ 2 x Baseline
- Any Instance of ALT ≥ 5 x ULN
- Any Instance of ALT ≥ 8 x ULN

Elevated Baseline ALT (ALT > ULN at Baseline):

- Any Instance of ALT ≥ 2 x Baseline and Total Bilirubin ≥2× Baseline
- Any Instance of ALT ≥ 3 x Baseline
- Any Instance of ALT ≥ 5 x Baseline

Subjects with post-baseline ALP values will be assessed for shift from Baseline ALP to the following DILI criteria:

- Any Instance of ALP ≥ 2 x Baseline and Total Bilirubin ≥ 2 x Baseline
- Any Instance of ALP ≥ 3 x Baseline

Summary results will include the count and percentage of subjects within each shift category, analyzed separately for each study treatment period and the study overall.

Subjects qualifying in any of the above ALT or ALP treatment-emergent DILI criteria will be presented in a data listing to include ALT (or ALP), baseline and treatment-emergent total bilirubin, baseline and treatment-emergent direct bilirubin, Gilbert Syndrome status, and any treatment-emergent AEs reported at the time of the treatment-emergent lab date.

The clinical study protocol also includes algorithms for monitoring and interrupting study drug for treatment-emergent acute deterioration of kidney function based on laboratory parameters or clinical symptoms. Any increase in serum creatinine by ≥0.3 mg/dL from baseline and any increase in serum creatinine to ≥1.5 x baseline will be summarized for each study period and the study overall.

4.5.6 Vital Signs, Physical Findings, and Other Observations Related to Safety

4.5.6.1 Vital Signs

Vital sign parameter measurements will be summarized by treatment group for each study treatment period. Descriptive statistics will be presented for results and change from baseline at each visit where parameters were scheduled to be collected. Change from the initiation of OLE will also be presented in the Open-Label Extension Period summary.

4.5.6.2 12-Lead Electrocardiogram

Twelve-Lead ECG interval parameters will be summarized by treatment group for each study treatment period. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected. Change from the initiation of OLE will also be presented in the Open-Label Extension Period summaries.

Twelve-lead ECG will be classified by the investigator as "normal," "abnormal, not clinically significant," or "abnormal, clinically significant." Three-by-three contingency tables will be presented to summarize the shift from the baseline category to the worst post-baseline value of each study treatment period and study overall. Shift from the initiation of OLE value to the worst post-OLE value will also be provided for the Open-Label Extension Period. Summary results will include the count and percentage of subjects within each shift category and treatment group for each study treatment period and study overall.

Prolonged QTc intervals will be summarized as QTc measurements (msec) that are >450, >480, and >500 at each visit where ECG is routinely collected per the clinical study protocol. Change from baseline categories will also be summarized for measurements that represent a change >30 or >60 relative to the baseline value. Change from the initiation of OLE will also be presented in the Open-Label Extension Period summary. Summary results will include the percentage of subjects within each category and treatment group for each study treatment period.

4.5.6.3 Physical Examination

Any clinically significant findings from the physical examination assessment will be reported on the Medical History form (prior to first dose) or Adverse Events form (post first dose). A separate subject listing of physical examination results will not be provided.

4.5.6.4 Crohn's Disease Activity Index (Crohn's Disease Subjects Only)

Crohn's Disease Activity Index total criteria point counts will be summarized by treatment group for each study treatment period for the subset of study subjects with CD. Descriptive statistics will be presented for results and change from baseline at each visit where parameters were scheduled to be collected. Change from the initiation of OLE will also be presented in the Open-Label Extension Period summary.

Additionally, the assignment of the CDAI scores into the disease severity categories of "asymptomatic remission (CDAI <150)," "mild-to-moderate CD (150 to 219)," "moderate-to-severe CD (220 to 450)," and "severe-fulminant disease (>450)." Four-by-four contingency tables will be presented to summarize the shift from the baseline category to the Week 6 and Week 12 categories (Open-Label Extension Period summary) for each study treatment period. For the Open-Label Extension Period summary, change from initiation of OLE to Week 12 will also be provided. Summary results will include the count and percentage of subjects within each shift category and treatment group for each study treatment period.

4.5.6.5 Partial Mayo Scoring Index (Ulcerative Colitis Subjects Only)

The Partial Mayo Scoring Index questionnaire categories (Bleeding, Stool Frequency, and Physician Assessment) and the total index score will be summarized by treatment group for each study treatment period for the subset of study subjects with Ulcerative Colitis. Summary results will include the count and percentage of subjects within each shift category and treatment group for each study visit where the questionnaire was collected.

Additionally, the total index score will be summarized as four-by-four contingency tables to present the shift from the baseline category to the Week 6 and Week 12 categories (Open-Label Extension Period summary) for each study treatment period. For the Open-Label Extension Period summary, change from Initiation of OLE to Week 12 will also be provided. Summary results will include the count and percentage of subjects within each shift category and treatment group for each study treatment period.

4.5.6.6 Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHO) Drug Global B3, version March 2022. Medications entered on the eCRF will be mapped to Anatomical Therapeutic Chemical (ATC) drug class (level 4) and drug name. The ATC drug class level 3 term is provided if level 4 is not available, and the ATC drug class level 2 term is provided if level 3 and level 4 are not available.

Prior and concomitant medications will be summarized separately and the study phase of each medication will be determined programmatically based on medication start and end dates. A prior medication is defined as any medication administered prior to the date of the first dose of study drug. A concomitant medication is defined as any medication administered on or after the date of the first dose of study drug. A medication may be defined as both prior and concomitant, and may occur in both study treatment periods based on reported start and end dates. If it cannot be determined whether a medication was received prior to the start of study drug dosing due to partial or missing medication start and/or end dates, it will be considered a prior medication. Likewise, if it cannot be determined whether a medication was received after the start of study drug dosing, it will be considered concomitant.

For both prior and concomitant medications summaries, the number and percentage of subjects receiving any medication will be summarized by treatment group, as will the number and percentage receiving any medication by ATC drug class and generic drug name. Concomitant medications will be summarized separately for the Double-Blind Treatment Period and Open-Label Extension Period. Prior medications will be summarized for the Full Analysis Set. Subjects reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. The ATC class terms will be displayed by descending order of incidence, as will generic drug names within each ATC class. Subjects receiving UDCA as part of their allowed treatment regimen will have the medication reported on the Prior and Concomitant Medication CRF for summarization in each applicable table. The study phase during which each medication was received (e.g., prior, concomitant, or both) will be presented on the listing of prior and concomitant medications, as well the study treatment period in which the medication

was received (e.g., Double-Blind Treatment Period, Open-Label Extension Period, or both). A listing of those concomitant medications that are prohibited and/or rescue medications and are to be considered intercurrent events for the primary estimand will also be provided.

4.6 Determination of Sample Size

Assuming a standard deviation of 2.5 points, a sample size of 26 subjects per treatment group provides approximately [redacted]% power to detect a [redacted] EP547 and placebo with respect to the change in weekly mean of the daily WI-NRS score based on a 2-sided, 2-sample comparison of means at the 5% significance level. With an anticipated early withdrawal rate of approximately 10%, the planned enrollment of 29 subjects per treatment group will ensure that at least 26 subjects complete the 6 weeks of double-blind treatment.

4.7 Changes in the Conduct of the Study or Planned Analyses

There were no changes to the study conduct or planned analyses identified within the development of this SAP, relative to the descriptions provided within the clinical study protocol.

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